CLINICAL PRACTICE

Secondary Prevention after Ischemic Stroke

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This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the authors' clinical recommendations.*

SUMMARY

The risk of recurrent ischemic stroke can be reduced by managing modifiable risk factors and instituting a regimen of mechanism-specific secondary stroke prevention. Strategies for secondary prevention should be instituted as early as possible. Poststroke monitoring of risk metrics, lifestyle behaviors, and medication recommendations is of key importance.

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CME

A 74-year-old man was transported to the emergency department by ambulance for sudden onset of weakness in the right side of his face and in his right arm and leg and slurred speech, which had begun 6 hours earlier. The National Institutes of Health Stroke Scale score was 4 (on a scale of 0 to 42, with higher scores indicating more severe neurologic impairment), and he had mild facial and upper and lower limb weakness and dysarthria on examination. A computed tomographic (CT) scan of the head was unremarkable, and a CT angiogram of the head and neck showed no stenosis or large-vessel occlusion. A magnetic resonance imaging (MRI) scan of the head later revealed a 1-cm infarct in the left posterior limb of the internal capsule, with hyperintensity on diffusion-weighted sequences. The patient has hypertension and hyperlipidemia treated with daily lisinopril (10 mg) and atorvastatin (10 mg), and his most recent glycated hemoglobin level was 6.5%. He is a nonsmoker, drinks alcohol occasionally, and maintains a healthy diet, but he has been less active in recent years because of joint pain. His body-mass index (the weight in kilograms divided by the square of the height in meters) is 32. How would you treat this patient to reduce his risk of another ischemic stroke?

THE CLINICAL PROBLEM

Ischemic stroke, defined as a central nervous system injury caused by loss of blood flow, is most often due to arterial thromboembolism.[1] Globally, the incidence of stroke was estimated at almost 12 million in 2021, with 94 million prevalent cases worldwide.[2] Stroke was the third leading cause of death and the fourth leading cause of healthy life-years lost. Each year, approximately 795,000 persons in the United States have a stroke, which is ischemic in 87%.[2] However, the incidence of ischemic and hemorrhagic stroke varies internationally, with almost 30% of all strokes in low- and middle-income countries being due to intracerebral or subarachnoid hemorrhage. The incidence of ischemic stroke sub-

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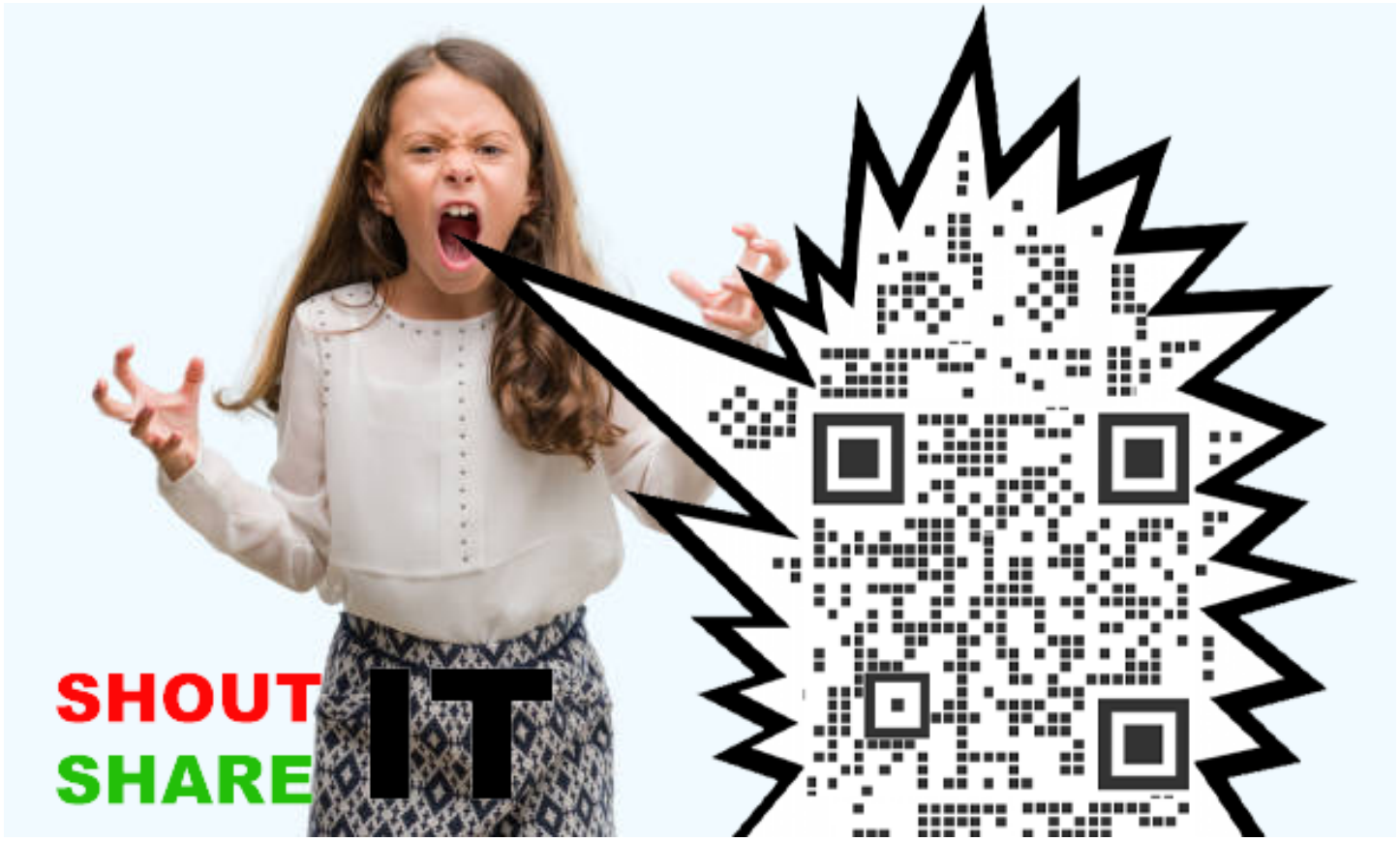
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types also varies internationally. For example, intracranial atherosclerosis is more frequently reported in Brazil and China, and lacunar stroke is more frequently described in China, Pakistan, and Taiwan.[3] Owing to population growth, increased life expectancy, and exposure to risk factors, the worldwide burden of stroke has almost doubled since 1990. The incidence among men and women is similar, although the prevalence is higher among women, which is possibly related to women's longer life expectancy.

The Global Burden of Disease Study 2016 showed that the top five risk factors for ischemic stroke were high systolic blood pressure, high low-density lipoprotein (LDL) cholesterol and fasting blood glucose levels, ambient particulate matter pollution, and smoking.[4] In the INTERSTROKE study, approximately 90% of the ischemic strokes were attributable to potentially modifiable risk factors (Fig. 1).[5]

Four main pathophysiological categories underlie ischemic stroke: large-artery atherosclerosis, cardioembolism, small-vessel disease, and cryptogenic stroke (which includes embolic stroke of undetermined source). The Trial of Org 10172 in Acute Stroke Treatment (TOAST) system describes classification criteria according to the presumed mechanism (Table 1).[6] The ASCOD (atherosclerosis [A], small-vessel disease [S], cardiac disease [C], other causes [O], dissection [D])[7] and Causative Classification of Stroke[8] systems further refine the probability of these mechanisms on the basis of available information after investigation.

Approximately 80% of patients with ischemic stroke return to community living. These patients have increased risks of recurrent stroke, myocardial infarction, and death from cardiovascular causes.[9] The risk of stroke recurrence is greatest in the first week but persists for years after the onset of the first stroke. A meta-analysis that included 138,000 patients showed that the annual risk of recurrent stroke was 4.3%, of myocardial infarction 0.9%, and of cardiac death 0.5%.[9] In the population-based Oxford Vascular Study, the 5-year risk of any stroke recurrence was 23% after cryptogenic stroke, 20% after small-vessel stroke, 23% after large-artery stroke, and 25% after cardioembolic stroke.[10] Increased risks of disability, death, dementia, and cognitive decline are common consequences of recurrent stroke. Modification of cardiovascular risk factors and mechanism-specific interventions may substantially reduce this risk.[11] Therefore, evaluation should include relevant blood tests and cardiovascular and cardiac investigations (Table 2).

STRATEGIES AND EVIDENCE

The approach to secondary stroke prevention includes lifestyle modification, pharmacologic treatment, and revascularization procedures for appropriately selected patients. The transition from hospital to community is an opportunity to initiate treatment early, which is associated with improved adherence to treatment and better outcomes.

STROKE-CARD was an open-label, randomized, controlled trial with blinded outcome assessment in which 2149 patients with acute transient ischemic attack (TIA) or stroke were assigned in a 2:1 ratio to receive the STROKE-CARD intervention or standard care.[12] The intervention was a disease-management program that comprised standardized visits every 3 months and Web-based patient support, including risk-factor management and education. At 12 months, recurrent major cardiovascular events occurred in 78 patients (5.4%) in the STROKE-CARD group and in 59 patients (8.3%) in the standard-care group (hazard ratio, 0.63, 95% confidence interval [CI], 0.45 to 0.88; P=0.007), although no meaningful difference in the composite of stroke or TIA was observed (in 6.3% and 6.5% of the patients, respectively). Quality of life as measured by the EuroQol 5-Dimensions 3-Levels (EQ-5D-3L) overall utility score was higher in patients in the STROKE-CARD group than in those in the standard-care group (P<0.001). These findings suggest that a structured program may be beneficial for improving overall cardiovascular outcomes in patients with recent stroke, even if the risk of stroke-specific outcomes is not reduced.

LIFESTYLE MODIFICATION

Continued smoking is associated with a doubling of the risk of stroke recurrence, and randomized trials of multibehavioral interventions after stroke have shown higher rates of smoking cessation than are seen with control.[13] Complete smoking cessation is advised, supported by nicotine-replacement therapy, counseling, and bupropion or varenicline therapy when appropriate.[14]

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In the medical group of the Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) trial, physical activity lasting at least 20 minutes at moderate-to-high intensity at least twice a week was independently associated with a 40% lower risk of recurrent cardiovascular events than less physical activity, as reported on the Physician-Based Assessment and Counseling for Exercise (PACE) questionnaire.[15] Although no high-quality stroke-specific trials exist on the topic of dietary changes, epidemiologic studies and randomized trials in high-risk patient groups indirectly support dietary interventions for the prevention of cardiovascular events after stroke. In the Prevención con Dieta Mediterránea (PREDIMED) trial, the risk of stroke among high-risk persons was lower with a Mediterranean-type diet enriched with olive oil or nuts than with a control diet (1.6% vs. 3.0%).[16] The American Heart Association recommends a Mediterranean-type diet (high in vegetables, fruit, grains, poultry, fish, low-fat dairy, olive oil, and tree nuts and low in processed foods, high-fat dairy products, and red meat) and a low-salt diet (<2.3 g per day).[17]

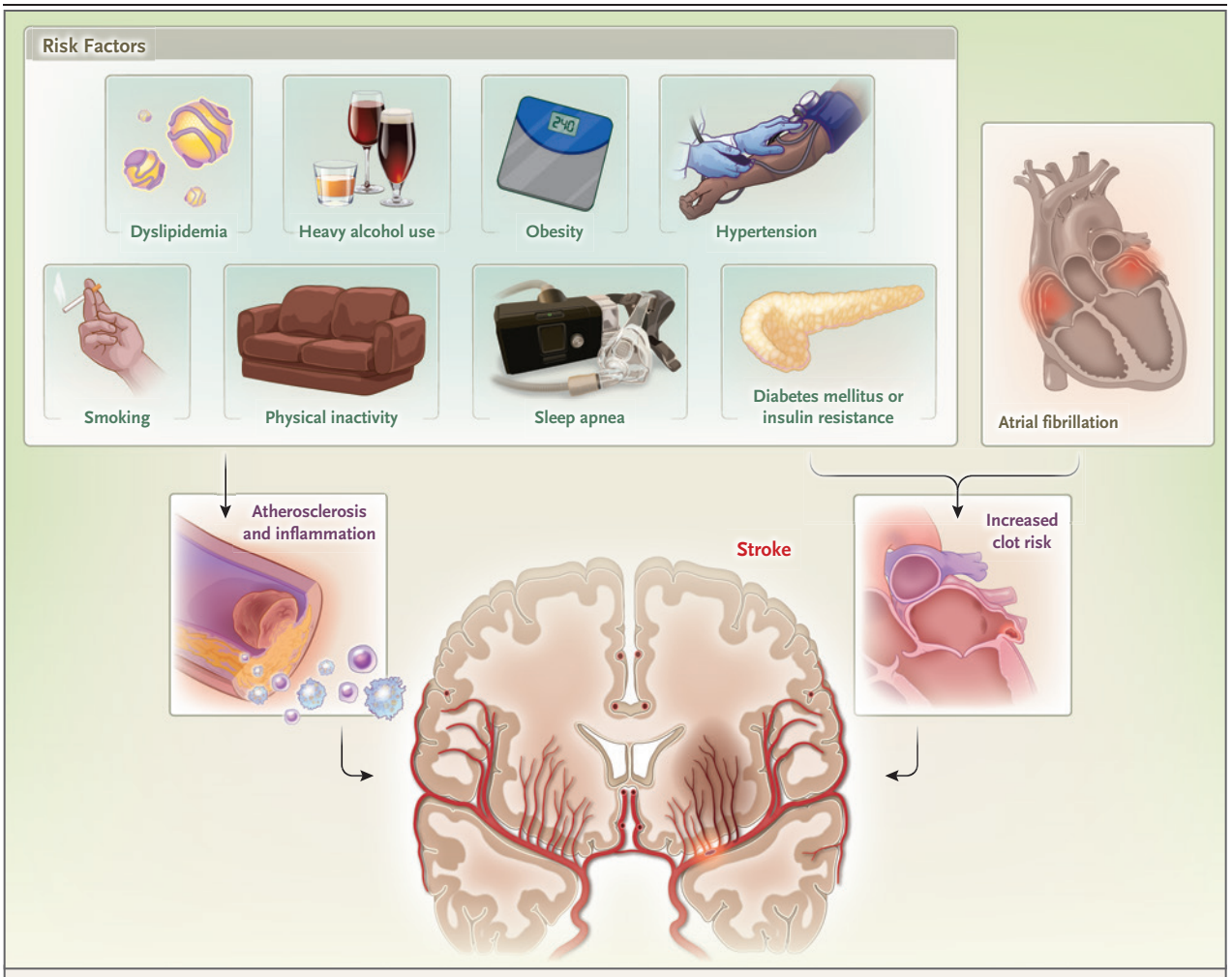

Figure 1. Pathophysiological Contributors to Stroke.

Interactions among vascular endothelium, flow dynamics, the inflammatory and coagulation systems, and structural cardiac disease contribute to stroke risk. Dyslipidemia, heavy alcohol use, obesity, hypertension, smoking, physical inactivity, sleep apnea, and diabetes mellitus or insulin resistance are all risk factors for stroke.

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MEDICAL MANAGEMENT

Antithrombotic Therapy

Randomized trials have shown a benefit of short-duration dual antiplatelet therapy (DAPT) for the prevention of early recurrent stroke in patients with noncardioembolic minor ischemic stroke (National Institutes of Health Stroke Scale score, ≤3) or high-risk TIA (Age, Blood Pressure, Clinical Syndrome, Duration–Diabetes [ABCD^2] score of ≥4, on a scale from 0 to 7, with higher scores indicating greater risk) in whom thrombolysis, thrombectomy, or carotid revascularization was not indicated.

In the Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke (POINT) trial (which included 4881 patients), aspirin plus clopidogrel begun within 12 hours after symptom onset and continued for 90 days led to a lower risk of major ischemic events than aspirin plus placebo (5.0% vs. 6.5%, P=0.02).[18] The Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events (CHANCE) trial showed that among patients who underwent randomization within 24 hours after an acute stroke, aspirin plus clopidogrel for 21 days followed by aspirin alone led to a lower risk of recurrent stroke within 90 days than aspirin alone (8.2% vs. 11.7%, P<0.001).[19] Pooled analyses of the trials indicated a maximal benefit of DAPT during the first 10 to 21 days after a stroke, with an increased risk of major bleeding seen with longer treatment durations.[20] The addition of ticagrelor to aspirin led to a lower risk of stroke or death than aspirin monotherapy at 90 days (5.5% vs. 6.6%, P=0.02), but the benefit was offset by an increased risk of fatal bleeding and intracerebral hemorrhage (0.4% vs. 0.1%).[21] In the Ticagrelor or Clopidogrel with Aspirin in High-Risk Patients with Acute Nondisabling Cerebrovascular Events II (CHANCE-2) trial, which included 6412 Chinese patients with acute minor stroke or TIA and *CYP2C19* loss-of-function alleles, DAPT with ticagrelor plus aspirin led to a lower risk of stroke at 90 days than DAPT with clopidogrel plus aspirin (6.0% vs. 7.6%, P=0.008).[22]

Monotherapy with aspirin or clopidogrel is usually continued after DAPT, on the basis of trial results that did not show the superiority of long-term DAPT over aspirin for late prevention.[23,24] Antiplatelet monotherapy with aspirin is recommended for long-term treatment in patients with symptomatic large-vessel intracranial stenosis (of 50 to 99%).[25]

In patients with cryptogenic stroke, prolonged cardiac monitoring with external or implantable monitors leads to better detection of atrial fibrillation than 24-hour monitoring.[26] Biomarkers

Table 1. Mechanisms of Ischemic Stroke.*

Large-artery atherosclerosis
Infarction in the territory of a stenotic (>50%) artery supplying the brain, attributed to atherosclerosis
Extracranial
Intracranial
Cardioembolism
Detection of a high- or medium-risk embolic source from the heart
Atrial fibrillation
Valvular disease (e.g., mechanical prosthetic valve or mitral stenosis)
Left ventricular thrombus
Cardiac myxoma
Endocarditis (infectious or marantic)
Patent foramen ovale or other intracardiac shunts
Small-vessel occlusion or lacunar stroke
Occlusion of a lenticulostriate, thalamogeniculate, basilar, or other perforator artery. Large-artery atherosclerosis and a cardioembolic source must be ruled out. CT scan or MRI may be normal, but a small (<1.5 cm) subcortical infarct supports the diagnosis.
Stroke of undetermined cause, including cryptogenic stroke or embolic stroke of undetermined source
No mechanism identified despite adequate investigation. Accounts for 30–40% of ischemic strokes. Potential causes include the following:
Aortic-arch atheroma
Atrial myopathy
Nonstenosing atherosclerotic plaque
Other determined cause of stroke
Less common conditions that may cause stroke include the following:
Dissection
Hypercoagulable state
Vasculitis
Migraine
Reversible cerebral vasoconstrictive syndrome
Genetic disorders (e.g., CADASIL or CARASIL)
Fabry's disease

* CADASIL denotes cerebral arteriopathy and subcortical infarct leukoencephalopathy, and CARASIL cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy.

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Table 2. Common Diagnostic Studies to Aid in Secondary Stroke Prevention.

Cardiovascular imaging
CT angiography, magnetic resonance angiography, or ultrasonography (carotid duplex ultrasonography and transcranial Doppler ultrasonography) to evaluate patency of the large arteries
High-resolution vascular-wall imaging, if indicated
Laboratory assessment
Total cholesterol, low-density and high-density lipoprotein cholesterol, and triglyceride levels; consider lipoprotein(a) level
Glycated hemoglobin
Glucose
Thrombophilia screen (in selected patients)
Imaging of the head
MRI
CT
Cardiac testing
12-Lead electrocardiogram
Telemetry
Prolonged ambulatory monitoring if embolism is suspected but the source is not identified
Transthoracic echocardiography
Transesophageal echocardiography or cardiac CT or MRI for suspected endocarditis, left atrial appendage thrombus, or aortic-arch atheroma

such as N-terminal pro–B-type natriuretic peptide (NT-proBNP) have been associated with atrial fibrillation burden but are not recommended in stroke guidelines.[27] In persons with established nonvalvular atrial fibrillation, thrombin or factor Xa inhibition with a direct oral anticoagulant (DOAC) is first-line therapy. A meta-analysis of randomized trials comparing a DOAC (dabigatran, apixaban, rivaroxaban, or edoxaban) with warfarin showed that the pooled risk of stroke or systemic embolism was 19% lower among patients treated with a DOAC (relative risk, 0.8; P<0.001).[28] The benefit was driven by a large reduction in the risk of hemorrhagic stroke, which was halved among patients treated with a DOAC, without a significantly lower risk of ischemic stroke. Secondary analyses of the practice-changing DOAC trials involving patients with previous stroke were consistent with the main trial results.[29]

Multiple trials have resolved uncertainty about the safety of early initiation of DOAC treatment after ischemic stroke. For example, in the OPTIMAS (Optimal Timing of Anticoagulation after Acute Ischaemic Stroke) trial, the early initiation of a DOAC (at ≤4 days) was noninferior to later treatment (at 7 to 14 days) in 3621 patients with atrial fibrillation and recent stroke with regard to a composite outcome of recurrent ischemic stroke, intracerebral hemorrhage, or systemic embolism at 90 days.[30] One quarter of the patients in that trial had paroxysmal atrial fibrillation. Patients with other high-risk cardioembolic sources, such as left ventricular thrombus, mechanical-valve replacement, or mitral stenosis, are generally treated with a vitamin K antagonist.

Hypertension

One meta-analysis of 14 randomized trials comparing more-intensive with less-intensive blood-pressure treatment in 42,736 patients with stroke or TIA showed that the pooled risk of recurrent stroke was 27% lower with more-intensive treatment (P<0.001) and the risk of death from cardiovascular causes was 15% lower (P=0.01).[17] Patients with a systolic blood pressure of less than 130 mm Hg had lower rates of stroke and death than those with higher systolic blood pressure (130 to 140 mm Hg or >140 mm Hg), and the extent of blood-pressure lowering was correlated with a lower risk of stroke. Long-term reductions in blood pressure can be achieved by a combination of lifestyle modifications and medication.

Hyperlipidemia

The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) randomized trial compared atorvastatin (80 mg daily) with placebo in 4731 patients with noncardioembolic ischemic stroke (67% of the patients), TIA (31%), or intracerebral hemorrhage (2%).[31] At a median follow-up of 4.9 years, the risk of recurrent stroke was 16% lower in the atorvastatin group than in the placebo group (adjusted hazard ratio, 0.84; P=0.03) and the risk of major cardiovascular events was 20% lower with atorvastatin (hazard ratio, 0.80; P=0.002). A higher risk of hemorrhagic stroke was observed in the atorvastatin group than in the placebo group (hazard ratio, 1.66; 95% CI, 1.08 to 2.55), but a net benefit in the prevention of ischemic events was observed. In a meta-analysis of randomized trials, for every 1000 patients with stroke who were treated, statin therapy was associated with an estimated 40 fewer ischemic major cardiovascular events

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and with 6 more hemorrhagic strokes — findings that indicated a net benefit of statin therapy.[32]

The Treat Stroke to Target trial, which involved 2860 patients with atherosclerosis and a previous stroke or TIA, showed that over a median follow-up of 3.5 years, patients who had been randomly assigned to a goal LDL cholesterol level of less than 70 mg per deciliter (1.8 mmol per liter) and received treatment with statin and ezetimibe as needed had an absolute risk of cardiovascular events (mainly ischemic stroke) that was 2.4 percentage points lower than those who had been assigned to a goal of 90 to 110 mg per deciliter (2.3 to 2.8 mmol per liter) (8.5% vs. 10.9%).[33] Although statins are generally safe, in a meta-analysis of randomized trials, the Cholesterol Treatment Trialists' Collaboration found an increased risk of diabetes that appeared to be dose-related (absolute risk increase of 0.1 percentage point per year with low- or moderate-intensity statin use and 1.3 percentage points per year with high-intensity statin use).[34]

Lifestyle changes and high-intensity statin therapy (e.g., atorvastatin at a dose of 40 to 80 mg or rosuvastatin at a dose of 20 to 40 mg) are recommended in order to reach a target LDL cholesterol level of less than 70 mg per deciliter. If the LDL cholesterol level remains elevated or if patients cannot take a statin, other LDL cholesterol–lowering agents (e.g., a proprotein convertase subtilisin–kexin type 9 [PCSK9] inhibitor, ezetimibe, or small-molecule interfering RNA therapies) may be indicated.[35,36] Some patients with hypertriglyceridemia may benefit from treatment with icosapent ethyl.[37,38] In a secondary analysis of the REDUCE-IT trial,[38] which involved 8179 patients with hypertriglyceridemia who were at high risk for ischemic events (71% of whom had a previous cardiovascular event), icosapent ethyl therapy led to a lower risk of fatal or nonfatal stroke than placebo (2.4% vs. 3.3%).

Diabetes

Type 2 diabetes mellitus is present in 30% of patients with ischemic stroke and is associated with an at least 50% higher risk of recurrent cardiovascular events.[39] Although no stroke-specific trials have been conducted in persons with type 2 diabetes, the target glycated hemoglobin level for persons with diabetes is less than 7%, with a level of 7 to 8% being a reasonable goal for those with a limited life expectancy or multiple coexisting conditions. Lifestyle behaviors such as weight loss or maintenance, exercise, and nonsmoking and metformin therapy should be prioritized in all patients. A meta-analysis involving 56,251 patients who had been included in eight randomized, placebo-controlled trials showed that glucagon-like protein-1 (GLP-1) receptor agonists led to 16% lower risks of nonfatal stroke (odds ratio, 0.84; P=0.002) and of any stroke (odds ratio, 0.84; P=0.001).[40] The evidence of benefit with sodium–glucose cotransporter 2 (SGLT2) inhibitors is best for the prevention of progression of kidney disease and heart failure, but these agents can be considered as an adjunct to metformin therapy in selected patients with stroke and diabetes.[41]

Carotid Revascularization: Endarterectomy and Stenting

Symptomatic atherosclerotic extracranial carotid-artery stenosis (50 to 99% lumen stenosis) benefits from revascularization with carotid endarterectomy or carotid-artery stenting.[42-44] A meta-analysis of 13 randomized, controlled trials that included 7484 patients with carotid stenosis (which was symptomatic in 80% of the patients) showed that stenting was associated with a higher risk of any stroke than carotid endarterectomy (relative risk, 1.45; 95% CI, 1.06 to 1.99) but with a lower risk of periprocedural myocardial infarction (relative risk, 0.43; 95% CI, 0.26 to 0.71).[45] Consideration of the choice of procedure should include technical feasibility, a risk–benefit assessment, and patient preference. Revascularization should typically occur within 2 weeks after symptom onset.[46] In patients with asymptomatic carotid stenoses of 50 to 99%, stenting, but not carotid endarterectomy, was found to be superior to medical management alone.[47]

GUIDELINES

Recommendations from the American Heart Association and the European Stroke Organization advise a target blood pressure of less than 130/80 mm Hg for most patients after ischemic stroke. In selected patients with noncardioembolic TIA or minor stroke, DAPT with aspirin and clopidogrel (initial dose of 300 mg, followed by 75 mg per day) or aspirin and ticagrelor

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KEY POINTS

SECONDARY PREVENTION AFTER ISCHEMIC STROKE

- After ischemic stroke, the risk of recurrence can be reduced by modifying risk factors related to the specific mechanism of stroke.
- Diagnostic studies help identify the mechanism of stroke and provide targets for intervention.
- Strategies for secondary prevention should be instituted as early as possible to improve adherence to therapy and prevent recurrence.
- Poststroke monitoring of risk metrics, lifestyle behaviors, and medication recommendations is of key importance.

(180 mg on day 1, followed by 90 mg twice daily) is recommended for 21 to 30 days and is generally followed by long-term antiplatelet monotherapy with aspirin or clopidogrel.[19,21,48] In patients with persistent or paroxysmal atrial fibrillation, DOAC therapy is appropriate. A target LDL cholesterol goal of less than 70 mg per deciliter is recommended. In patients with type 2 diabetes, a target glycated hemoglobin level of less than 7% is generally advised, along with modifications in lifestyle behaviors associated with cardiovascular risk, metformin therapy, and the addition of either a GLP-1 agonist or an SGLT2 inhibitor.

AREAS OF UNCERTAINTY

Although inflammation contributes to stroke risk, the role of antiinflammatory agents for secondary stroke prevention remains unclear.[49] Sleep apnea is a well-established risk factor for stroke, but whether treatment after stroke reduces recurrence is unclear.[50] Ongoing trials (e.g., ClinicalTrials.gov numbers, NCT05963698 and NCT04394546) are evaluating strategies for left atrial appendage occlusion in patients with atrial fibrillation who are at high bleeding risk.[51,52] The use of DAPT for symptomatic high-grade intracranial atherosclerotic disease remains uncertain, as does effective therapy for carotid- and vertebral-artery dissection, aortic-arch atheroma, and patent foramen ovale in older adults.

CONCLUSIONS AND RECOMMENDATIONS

The patient described in the vignette has a lacunar ischemic stroke with multiple cardiovascular risk factors and evidence of insulin resistance. We would prescribe aspirin and clopidogrel for 21 days, followed by aspirin at a dose of 81 mg daily thereafter, and would intensify his blood-pressure treatment with indapamide to reach a blood pressure of less than 130/80 mm Hg. We would also favor increasing his lipid-lowering therapy to meet an LDL cholesterol goal of less than 70 mg per deciliter, initially with the dose of atorvastatin increased to 80 mg per day. We would counsel the patient on lifestyle management, including a structured weight-loss program. Ongoing monitoring of adherence to therapy and prevention goals is important.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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